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DATA EVALUATION RECORD[1]

STUDY TYPE: Prenatal Developmental Toxicity Study - Rat; OPPTS 870.3700a [§83-3a]; OECD 414.

PC CODE: 016331 **DP BARCODE:** D410187

TEST MATERIAL (PURITY): Momfluorothrin (95.7% a.i.)

SYNONYMS: S-1563

CITATION: Izumi, H. (2011) Study on the Effect of Oral Administration of S-1563 on Embryo-Fetal Development in Rats. Kumamoto Laboratory. Uto-shi, Japan. Study No. P081121, March 23, 2011. MRID 49020016. Unpublished

SPONSOR: Sumitomo Chemical Co., Ltd.

EXECUTIVE SUMMARY:

In a developmental toxicity study (MRID 49020016) momfluorothrin (S-1563) (95.7% a.i., batch/lot 9CM0109G) was administered to female Sprague-Dawley rats (24/dose) by gavage at dose levels of 0, 10, 25, or 75 mg/kg/day from days 6 through 19 of gestation.

No treatment related effects on mortality, body weights or food consumption or gross pathology were reported. Tremors were observed in 6 dams of the 75 mg/kg/day group. Tremors occurred in 1-2 dams per day on days 15, 17, 18, and 19 of gestation and occurred at 2 to 3 hours after administration or between 4:00 and 5:00 in the afternoon.

The maternal LOAEL is 75 mg/kg bw/day, based on tremors in dams at the high-dose. The maternal NOAEL is 25 mg/kg bw/day.

No significant effects were observed between the control group and treatment groups regarding the number of implantations, rate of pre-implantation loss, post-implantation loss, early resorptions, late embryonic death and dead fetuses, number of live fetuses, sex ratio, or body weight of live male and female fetuses. No effects were observed when compared to controls on external, visceral or skeletal examinations.

The developmental NOAEL is 75 mg/kg bw/day.

1 Disclaimer: The attached Data Evaluation Record is a modified version of the Tier II Summary provided by Sumitomo Chemical Co. Ltd. Portions of this document may have been altered by the EPA reviewer.

The developmental toxicity study in the rat is classified as **Acceptable Guideline***;* and satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; OECD 414) in the rat. The lack of stability data was noted as a minor deficiency. However, this is not expected to impact the results of the study.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material	Momfluorothrin
Description:	Yellow solid
Lot/Batch:	9CM0109G
Purity:	95.7%
CAS#:	609346-29-4
Stability:	Expiry date 07 Sept 2010 (after completion of administration)
2. Vehicle	Corn oil
3. Test Animals	
Species	Rat
Strain	Crl:CD(SD)
Age	12 weeks (at start of mating)
Weight	230.7 – 294.9 g
Source	Charles River Laboratories, Japan Inc
Acclimation period	The quarantine/acclimatization period was 13 days for female animals received at the age of 10 weeks and 20 days for female animals received at the age of 9 weeks.
Diet	Pellet diet (CRF-1, Oriental Yeast Co.)
Water	Well water *ad libitum*
Housing	Stainless steel cages (226 mm (W) x 346 mm (D) x 198 mm (H))
Environmental conditions	
Temperature	24.2 – 25.8ºC (acceptable range: 20 – 26 ºC (21 – 27 ºC until September 30, 2010))
Humidity	49.5 – 69.8% (acceptable range: 35 – 75%)
Air change	10 – 20 air changes per hour
Photoperiod	12 hour light / dark cycle

B. PROCEDURES AND STUDY DESIGN

1. **In life dates:** 16 August 2010 – 12 July 2012

2. **Mating:** 12-week old nulliparous female and male animals were housed in the same cage overnight. Confirmation of mating was determined by the presence of sperm in the vaginal washing or the presence of a copulatory plug and was designated as day 0 of gestation.

3. **Animal assignment:** Animals were assigned by body weight stratification to dose groups as indicated in Table 1.

TABLE 1. Animal assignment

Dose (mg/kg bw/day)	0	10	25	75
Number of Females	24	24	24	24

4. **Dose selection rationale:** The dose levels were selected based on the results from a range-finding study where oral - administration of up to 300 mg/kg/day resulted in tremors and death. In the 75 mg/kg group death was only observed in one animal. Based on the above results the HDT was set at 75 mg/kg/day.

5. **Dosage preparation and analysis:** Dosing solutions were prepared at a frequency of once or twice per week and used within 7 days after preparation. Test material-vehicle mixture was prepared by mixing appropriate amounts of test substance with corn oil and then stored at 3.6 to 6.8ºC. Prior to the start of the study, stability of the test substance in corn oil was evaluated for a period of 15 days at 1 to 15ºC. Concentration and homogeneity (top, middle, and bottom) of the test mixture were evaluated weekly.

Results:
Homogeneity analysis: Samples for concentration analysis were collected from 2 arbitrary sites in each dosing solution. No apparent differences between dose sites were identified.

Stability analysis: Reported as stable for 15 days under refrigerated conditions and 6 hours at room temperature (data not provided).

Concentration analysis (% nominal): 97.8 to 100.3

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the study animals was acceptable.

6. **Dosage administration:** All doses were administered once daily by oral gavage, on gestation days 6 through 19, in a volume of 5 mL/kg of body weight/day. Dosing was based on the body weight on the most recent body weight determination.

C. OBSERVATIONS:

1. Maternal observations and evaluations: The animals were checked for mortality or clinical signs three times daily during the administration period, and once per day outside of the administration period. . Body weight and food consumption data were recorded on days 0, 3, 6, 9, 12, 15, 18, and 20 of gestation. On day 20 of gestation, pregnant females were sacrificed by i.v. pentobarbital injection and exsanguination. Gross examination of thoracic and abdominal viscera was made. The uterus including ovaries was removed. Isolated ovary and uterus (including cervical region) were weighed (gravid uterus weight measurement), followed by counting of the number of corpora lutea, implantations sites, early resorptions, late resorptions, dead fetuses, and live fetuses. In addition, gross observation of the placenta was performed. Live fetuses were measured for body weight and identified for sex, and examined for external anomalies macroscopically and under a stereoscopic microscope. Early resorptions, late resorptions, and dead fetuses were recorded.

Uteri with no macroscopically detectable implantations were immersed in 2% potassium hydroxide for at least 5 hours to check the presence or absence of implantations. As a result, no implantations were detected in any of the animals without macroscopically detectable implantations. These animals were therefore judged to be non-pregnant.

2. Fetal evaluations: Sex identification and observation of external anomalies were performed under blinded conditions. Approximately half of the live fetuses (including those with external anomalies) were assigned to visceral examination and the other half to skeletal examination. The fetuses assigned for visceral examination were fixed in Bouin's fluid, and stored. The fetuses assigned for skeletal examination were identified by tattooing the limbs, fixed in 70 vol% ethanol, and stored.

From the fetuses immersed and fixed in 70 vol% ethanol, transparent skeletal preparations stained with alizarin red S were prepared according to the method of Staples, and were observed for skeletal anomalies, skeletal variations, and progress of ossification under a stereoscopic microscope. The progress of ossification was evaluated using the number of the sacrococcygeal centrums, vertebral arches, and the sternebrae as the indices. All examinations were performed blind. After examination, fetuses were stored in 100 vol% glycerol.

The fetuses immersed and fixed in Bouin's fluid were examined for the cranial and abdominal regions according to Wilson's razor blade section method, and for the thoracic region according to Nishimura's micro-dissection method. The examinations were performed blind. After the examinations, the fetuses were stored in Bouin's fluid again.

D. DATA ANALYSIS:

1. **Statistical analyses:** Statistical analyses were performed using a computer system (MiTOX-PPL, Mitsui Zosen Systems Research Inc.). All analyses were performed with a two-sided significance level of 1% or 5%. Nonpregnant animals were excluded from evaluation. The mean and standard deviation were calculated for each group and homogeneity of variance tested according to the method of Bartlett (significance level: 5%). If the variance was homogeneous, comparison with the control group was performed using Dunnett's multiple comparison. If the variance was not homogeneous, comparison with the control group was performed using Steel's multiple comparison. The sex ratio: number of live male fetuses/number of live female fetuses was analyzed using the Chi squared test. A Wilcoxon rank sum test was used to evaluate implantation loss, resorption rate, dead fetuses, external anomalies, placental anomalies, visceral anomalies, skeletal anomalies, and skeletal variations.

2. **Indices:** The following indices were calculated from cesarean section records of animals in the study: Rate of pre-implantation loss: [(number of corpora lutea – number of implantations) / number of corpora lutea] × 100; Rate of post-implantation loss: [(number of implantations – number of live fetuses) / number of implantations] × 100.

3. **Historical control data:** Historical control data were provided to allow comparison with concurrent controls for visceral examinations.

II. RESULTS:

A. MATERNAL TOXICITY:

1. **Mortality and clinical observations:** Tremors were observed in 6 dams of the 75 mg/kg/day group. Tremors occurred in 1-2 dams per day on days 15, 17, 18, and 19 of gestation and occurred at 2 to 3 hours after administration or between 4:00 and 5:00 in the afternoon. Tremors did not persist to the next day.

2. **Body weight:** Body weight data are summarized in Table 2 and as follows: No significant changes in body weight occurred throughout the treatment period at any dose level. A slight decrease in body weight gain was reported on gestation day 20 for mid and high-dose dams. However, no effects on overall bodyweight, or corrected body weight gain were identified.

TABLE 2. Mean (±SD) maternal body weight and body weight gain (g) [a]

Interval	Dose in mg/kg bw/day (# of Dams)			
	Control (23)	10 (22)	25 (23)	75 (24)
Pre-treatment				
Day 0	263.8 ± 14.8	262.1 ± 14.8	263.6 ± 10.0	263.1 ± 14.1
Day 3	281.0 ± 17.6	278.5 ± 17.6	281.6 ± 11.2	280.4 ± 15.4
Treatment				
Day 6	294.4 ± 16.4	292.9 ± 17.3	293.6 ± 11.3	292.9 ± 15.3
Day 9	305.1 ± 18.4	303.0 ± 18.2	303.7 ± 12.6	302.8 ± 16.5
Day 12	321.5 ± 20.5	320.1 ± 19.9	317.6 ± 13.7	318.6 ± 17.9
Day 15	338.7 ± 21.3	338.3 ± 20.9	334.6 ± 12.3	335.3 ± 17.5
Day 18	380.6 ± 23.3	379.5 ± 24.6	372.6 ± 12.8	372.7 ± 19.0
Post-treatment				
Day 20	412.6 ± 24.9	410.2 ± 27.6	401.9 ± 12.6	401.0 ± 20.5
Corrected BW Gain (Day 20)	40.8 ± 8.3	40.1 ± 11.0	33.3 ± 9.8	36.8 ± 13.1

[a] Data obtained from pages 38 to 40 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

3. **Food consumption:** Food consumption data are summarized as follows: In the high dose, a slight decrease in food consumption was observed on gestation days 6, 15, 18, and 20. Mid-dose dams also showed a slight decrease on days 15 and 20.

4. **Gross pathology**: No abnormalities were observed at any dose level.

5. **Cesarean section data:** No significant effects were observed between the control group and treatment groups regarding the number of implantations, rate of pre-implantation loss, post-implantation loss, early resorptions, late embryonic death and dead fetuses, number of live fetuses, sex ratio, or body weight of live male and female fetuses. A slight but statistically significant decrease in the number of corpora lutea was recorded in the high-dose group; however, this was not considered to be related to treatment with the test substance since the design of the study is such that dosing does not begin until after implantation has already occurred.

TABLE 3 Cesarean section observations [a]

Observation	Dose (mg/kg bw/day)			
	0	**10**	**25**	**75**
# Animals assigned (mated)	24	24	24	24
# Animals pregnant	23	22	23	24
Total No. corpora lutea **Mean ± s.d.**	354 15.36 ± 1.64	332 15.09 ± 1.51	339 14.74 ± 1.21	341 14.21 ± 1.25*
Total No. implantations **Mean ± s.d.**	339 14.74 ± 1.74	314 14.23 ± 1.38	329 14.30 ± 1.26	329 13.71 ± 1.49
Total No. live fetuses **Mean ± s.d.**	328 14.26 ± 1.74	299 13.59 ± 2.87	310 13.48 ± 2.35	311 12.96 ± 1.90
Total No. dead fetuses **(Dead fetuses/dam)**	0	0	0	0
Total No. resorptions	11	15	19	18
Early	11	15	19	17
Late	0	0	0	1
Mean fetal weight (g):				
Males	3.71 ± 0.32	3.83 ± 0.24	3.77 ± 0.31	3.76 ± 0.20
Females	3.54 ± 0.27	3.64 ± 0.32	3.59 ± 0.28	3.53 ± 0.27
Sex ratio male:female	0.99	0.88	0.88	0.97
Preimplantation loss (%)	4.24	5.42	2.95	3.52
Postimplantation loss (%)	3.24	4.78	5.78	5.47

[a] Data obtained from page 44 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

B. DEVELOPMENTAL TOXICITY:

1. **External examination**: No treatment related effects were identified when compared to controls.

2. **Visceral examination:** No treatment related effects were identified when compared to controls.

3. **Skeletal examination:** No treatment related effects were identified when compared to controls.

TABLE 4a. External examinations [a]

Observations	Dose (mg/kg bw/day)			
	0	**10**	**25**	**75**
No. Fetuses examined	328	299	310	311
No. Fetuses affected	1	0	1	0
Anal atresia	1	0	1	0
Vestigial tail	1	0	1	0

[a] Data obtained from page 44 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

TABLE 4b. Visceral examinations [a]

Observations	Dose (mg/kg bw/day)			
	0	**10**	**25**	**75**
#Fetuses examined	170	152	161	162
#Fetuses affected	11	12	11	12
Ventricular septal defect	0	1	0	0
Dilation of the renal pelvis	7	4	4	2
Dilation of the ureter	11	10	6	10
Thymic remnant in the neck	0	0	5	2

[a] Data obtained from page 45 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

TABLE 4c. Skeletal examinations [a]

Observations	Dose (mg/kg bw/day)			
	0	**10**	**25**	**75**
#Fetuses examined	158	147	149	149
# of fetuses with skeletal anomalies	2	0	0	0
# of fetuses with skeletal variations	25	22	23	23

[a] Data obtained from page 46 in the study report.
* Statistically different ($p < 0.05$) from the control.
** Statistically different ($p < 0.01$) from the control.

III. DISCUSSION AND CONCLUSIONS:

A. INVESTIGATORS' CONCLUSIONS: Observation on cesarean section showed that the test substance had no effect on the rate of post-implantation loss (rates of early resorption, late resorption, and dead fetuses) or the number of live fetuses, indicating that the test substance did not have lethal effect on embryos or fetuses. Gross observation of the placenta detected no abnormalities. Morphological examination of fetuses (external, visceral, and skeletal examinations) showed no anomalies or variations induced by the administration of the test substance, demonstrating that the test substance had no teratogenic activity. Also, the test substance had no effect on the body weight of live fetuses, progress of ossification, or development of fetuses.

Thus, although tremors were observed in dams of the 75 mg/kg group, administration of the test substance had no effect on the reproductive function of dams or on the embryo-fetal development. Based on the above results, the no observed adverse effect level of S-1563 was estimated to be 25 mg/kg/day for dams in terms of general toxicity and 75 mg/kg/day for the reproductive function of dams and for embryo-fetal development.

B. REVIEWER COMMENTS: S-1563 had no effect on embryo-fetal development. The NOAEL for developmental toxicity is 75 mg/kg. The maternal LOAEL is 25 mg/kg based on tremors observed in dams at the high-dose. The NOAEL is 25 mg/kg.

C. STUDY DEFICIENCIES: Minor deficiency: Stability data not provided.